Title: A Randomized, Open-Label, Single-Dose, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of TAK-438 OD (Orally Disintegrating) 20 mg Tablet When Administered without Water (Study 1) or with Water (Study 2) and TAK-438 20 mg Tablet When Administered with Water in Japanese Healthy Volunteer Male Subjects

NCT Number: NCT03808493

Protocol Approve Date: 12-DEC-2018

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Open-Label, Single-Dose, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of TAK-438 OD (Orally Disintegrating) 20 mg Tablet When Administered without Water (Study 1) or with Water (Study 2) and TAK-438 20 mg Tablet When Administered with Water in Japanese Healthy Volunteer Male Subjects

A Phase 1 Bioequivalence Study of TAK-438 OD tablet

Study Identifier: TAK-438ODT-1001

Compound: TAK-438ODT

Date: 12 December 2018

Version/Amendment Number: Initial Version

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CCI [redacted]

1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceuticals Company Limited	**Compound:** TAK-438 OD Tablet TAK-438 tablet
Study Identifier: TAK-438ODT-1001	**Phase:** 1
Protocol Title: A Randomized, Open-Label, Single-Dose, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of TAK-438 OD (Orally Disintegrating) 20 mg Tablet When Administered without Water (Study 1) or with Water (Study 2) and TAK-438 20 mg Tablet When Administered with Water in Japanese Healthy Volunteer Male Subjects	
Trial Design: This study which consists of two studies, Study 1 and Study 2, is a pharmacokinetic (PK) study in healthy Japanese subjects to evaluate the bioequivalence (BE) of single oral dose of TAK-438 OD 20 mg tablet without water and TAK-438 20 mg tablet with water (Study 1), and TAK-438 OD 20 mg tablet with water and TAK-438 20 mg tablet with water (Study 2) in an open-label and crossover (2x2) design. The safety of single oral dose of TAK-438 OD 20 mg tablet, and TAK-438 20 mg tablet under fasted conditions will be also evaluated. Pilot and Pivotal BE studies are planned for Study 1 and Study 2 in accordance with the "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No.0229-10 dated 29 February 2012) as follows; Pilot and Pivotal BE studies will be conducted in the same design (inclusion/exclusion criteria, dose, regimen and schedule). Pilot BE studies will be conducted first for the sample size estimation to demonstrate the bioequivalence in Pivotal BE studies. The data from Pilot BE studies can be merged with the data from Pivotal BE study as needed when the bioequivalence is evaluated. Pivotal BE studies will not be conducted in the case the bioequivalence is demonstrated in Pilot BE study, or the results from Pilot BE study indicate that it is not feasible to demonstrate the bioequivalence. In the Pilot BE study, 24 subjects will be enrolled in each study (12 subjects in each treatment sequence). Subjects will be randomly assigned to either Treatment Sequences with 1:1 allocation in each study. In the Pivotal BE study, 26 to 48 subjects will be enrolled in each study (13 to 24 subjects in each treatment sequence depending on outcome of the pilot BE study). Subjects will be randomly assigned to either Treatment Sequences with 1:1 allocation in each study. In each treatment sequence of Pilot and Pivotal BE studies, subjects will receive a single dose of either of TAK-438 OD 20 mg tablet without water or TAK-438 20 mg tablet with water (Study 1), and either of TAK-438 OD 20 mg tablet with water or TAK-438 20 mg tablet with water (Study 2) on Day 1 in Periods 1 and 2. If a subject discontinues from the study, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor. The study site should contact the sponsor for the replacement of subject's treatment assignment and medication identification number.	
Trial Primary Objective: To evaluate the bioequivalence of a single oral administration of a TAK-438 OD 20 mg tablet without water in comparison with TAK-438 20 mg tablet (Study 1), and TAK-438 OD 20 mg tablet with water in comparison with TAK-438 20 mg tablet (Study 2) in Japanese healthy male subjects. **Secondary Objective:** To assess the PK parameters other than AUC_{last} and C_{max} of TAK-438F in Japanese healthy male subjects who take TAK-438 20 mg.	
Trial Subject Population: Healthy Japanese adult male subjects, aged 20 to 60 years, inclusive.	

Planned Number of Subjects:	**Planned Number of Sites:**
For Study 1 and Study 2: Pilot study: 12 per sequence, 24 in total Pivotal study: 13 to 24, 26 to 48 in total Up to approximately 144	1 site
Dose Levels: Study 1: One TAK-438 OD 20 mg tablet without water or one TAK-438 20 mg tablet taken orally with 150 mL of water under fasted (without breakfast [after at least 10 hours of fasting]) condition. Study 2: One TAK-438 OD 20 mg tablet or one TAK-438 20 mg tablet taken orally with 150 mL of water under fasted (without breakfast [at least 10 hours of fasting]) condition	**Route of Administration:** Oral
Duration of Treatment: Study 1: Single oral administration (TAK-438 OD 20 mg tablet or TAK-438 20 mg tablet) in Periods 1 and 2 Study 2: Single oral administration (TAK-438 OD 20 mg tablet or TAK-438 20 mg tablet) in Periods 1 and 2	**Planned Trial Duration:** From the day before study drug administration through 48 hours after administration in Periods 1 and 2

Main Criteria for Inclusion:

1. In the opinion of the investigator or sub-investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject is a healthy Japanese adult male, aged 20 to 60 years, inclusive, at the time of informed consent.
4. The subject weighs at least 50 kg and has a body mass index (BMI) from 18.5 to 25.0 kg/m^2, inclusive at Screening.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months prior to the start of study drug administration in Period 1.
6. The subject must be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead electrocardiogram (ECG), and vital sign measurements performed at the Screening Visit and prior to the start of study drug administration in Period 1.

Main Criteria for Exclusion:

1. The subject has received any investigational compound within 16 weeks (112 days) prior to the start of study drug administration in Period 1.
2. The subject has received TAK-438 in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member of or a study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, or endocrine disease or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate in the study or potentially confound its results.
5. The subject has hypersensitivity to any component of TAK-438 OD tablet or TAK-438 tablet.
6. The subject has a positive urine drug result for drugs of abuse at Screening.

7. The subject has a history of drug or alcohol abuse within 2 years prior to the Screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
8. The subject has taken any excluded medication, supplements, or food products during the time periods.
9. The subject has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis), frequent (more than once per week) occurrence of heartburn, or any surgical intervention.
10. The subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1.
11. The subject has a positive test result for hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, or serological reactions for syphilis at Screening.
12. The subject has poor peripheral venous access.
13. The subject has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of study drug administration in Period 1.
14. The subject has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of study drug administration in Period 1.
15. The subject has undergone blood component collection within 2 weeks (14 days) prior to the start of study drug administration in Period 1.
16. The subject has a Screening or Check-in (Day -1) ECG that was abnormal (clinically significant).
17. The subject has abnormal Screening laboratory values that suggest a clinically significant underlying disease or subject with the following laboratory abnormalities: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above the upper limits of normal (ULN).
18. The subject who, in the opinion of the investigator or sub-investigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the study is:

PK (plasma concentration)

AUC_{last} and C_{max} of TAK-438F.

The secondary endpoints of the study are:

PK (plasma concentration)

AUC_{∞}, t_{max}, $MRT_{\infty,ev}$, and λ_z of TAK-438F.

Safety:

Treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, weight, and 12-lead ECG.

Statistical Considerations:

PK:

The following analyses will be separately conducted for each study (Study 1 and Study 2) based on the PK analysis set.

Analytical methods:

1) Plasma concentrations

   At each time point scheduled for blood sampling, descriptive statistics of plasma concentrations of TAK-438F will be provided for each formulation (ie, TAK-438 OD tablet and TAK-438 tablet). Case plots and mean plots with standard deviations (SD) will be provided for each formulation. Descriptive statistics of PK parameters will be provided for each formulation. Additionally, descriptive statistics will be provided for AUC_{last} and C_{max} ratios (TAK-438 OD tablet/TAK-438 tablet).

2) Bioequivalence assessment

For log-transformed (natural log) AUC_{last} and C_{max} of TAK-438F (ie, the primary endpoint of the study), the two-sided 90% confidence interval (CI) of the difference in the least square means between the formulations (TAK-438 OD tablet − TAK-438 tablet) will be provided using the analysis of variance (ANOVA) model. The same analyses will be performed for untransformed AUC_{last} and C_{max}.

The same analyses will also be performed for AUC_{∞}, tmax, $MRT_{\infty. ev}$, and λ_z to provide additional information. (ie, the secondary endpoints of the study).

Safety:

The following analyses will be separately conducted for each study (Study 1 and Study 2) based on the safety analysis set.

Analytical methods:

1) TEAEs

A TEAE is defined as an AE with a date of onset that occurs on or after the start of study drug administration. Frequency distribution of TEAEs will be provided for all TEAEs, drug-related TEAEs, TEAEs by intensity, drug-related TEAEs by intensity, and serious TEAEs for each formulation. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and tabulated by system organ class (SOC) and preferred term (PT) for each formulation.

2) Clinical laboratory tests, vital signs, weight, and 12-lead ECG

For continuous variables in clinical laboratory tests, vital signs and ECG parameters, descriptive statistics of observed values and changes from baseline will be provided for each scheduled time point by formulation. For categorical variables in clinical laboratory tests and ECG parameters, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled time point will be provided for each formulation.

Sample Size Justification:

For each of the studies (Study 1 and Study 2), the planned number of subjects is 12 per sequence (total of 24 subjects) in the pilot study, and a maximum of 24 per sequence (total of 48 subjects) in the pivotal study. Statistical basis for the sample size is presented below.

Assuming a root mean square error of 0.195 for PK parameters in the pilot study, the power of two one-sided t-tests to verify the bioequivalence [H_0: $\ln(\mu)\leq\ln(\theta_1)$, $\ln(\mu)\geq\ln(\theta_2)$; H_1: $\ln(\theta_1)<\ln(\mu)<\ln(\theta_2)$; where $\mu=\mu_t/\mu_s$, μ_t is the mean for TAK-438 OD tablet, μ_s is the mean for TAK-438 tablet, $\theta_1=0.80$, and $\theta_2=1.25$] at a one-sided significance level of 5% and $\mu=0.95$ to 1.05 would be ≥90% with a sample size of 12 subjects per sequence (total of 24 subjects).

In the case that the pivotal study will be implemented, the number of subjects will be recalculated based on the results from the pilot study. Assuming a maximal root mean square error of 0.195 for PK parameters in preceding studies of TAK-438, two one-sided t-tests with a one-sided significance level of 5% and $\mu=0.90$ to 1.11 would need a maximum of 24 subjects per sequence (total of 48 subjects) to provide 90% power to verify the bioequivalence.

2.0 STUDY SCHEMATIC

Figure 2.a Schematic of the Study Design (Studies 1 and 2, with 7-day Washout Period)

Element	Screening	Period 1					Period 2			
Study Day	-28 to -2	-1	1	2	3		8	9	10	11
Visit/ Confinement	Visit	Confinement					Confinement			
Procedure	Informed consent Screening tests	Check-in/Examinations	Examinations/Randomization Administration of study drug for Period 1	Examinations	Examinations/Discharge	Washout	Check-in/Examinations	Administration of study drug for Period 2//Examinations	Examinations	Examinations/Discharge

3.0 SCHEDULE OF STUDY PROCEDURES (STUDIES 1 AND 2)

	Screening Period	Check in	Treatment Period															ET
Study Day	**-28 to -2**	**-1[a]**	**1 to 3**															
Scheduled Time (Hours)			**Pre-dose**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**24**	**36**	**48**	
Administrative Procedures																		
Informed consent	X																	
Inclusion/exclusion criteria[d]	X	X	X															
Medical history/ demographics	X																	
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments																		
Physical examination	X	X	X														X	X
Weight, height and BMI	X	X[b]															X[b]	X[b]
Vital signs	X	X	X														X	X
Safety ECG	X	X															X	X
Study drug administration			X															
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments																		
Hematology, Chemistry and Urinalysis	X		X														X	X
Urine drug screen	X																	
HIV and Hepatitis screen	X																	
PK Evaluations																		
Plasma sample for TAK-438			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
Other																		
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AE, adverse event; BMI, body mass index; ECG, electrocardiogram; ET, early termination; PK, pharmacokinetic(s)
a 18 hours prior to dosing
b Only weight
c Plasma samples for TAK-438 PK evaluations should be collected only in the case of early termination within 48 hours after the study drug administration
d At Screening and prior to the administration of study drug on Period 1. It will not be conducted on Day 1 (the day of the administration of the study drug on Period 2).

4.0 INTRODUCTION

4.1 Background

TAK-438 is a novel class of stomach acid suppressants, referred to as a potassium-competitive acid blocker (P CAB). The efficacy and safety of TAK-438 were established in the clinical studies in patients with acid-related diseases. TAK-438 10 mg and 20 mg tablets were approved in December 2014 in Japan, indicated for erosive esophagitis (including a maintenance treatment of erosive esophagitis), gastric ulcer, duodenal ulcer, prevention of recurrent gastric or duodenal ulcer during low-dose aspirin therapy, prevention of recurrent gastric or duodenal ulcer during non-steroidal anti-inflammatory drug (NSAID) therapy, and adjunct to Helicobacter pylori (H. pylori) eradication.

TAK-438 10 mg and 20 mg tablet is widely used in elderly patients. A formulation with easier administration is preferable in Japan, super-aging society, because patients with decreased deglutition function exist. TAK-438 OD tablet is rapidly disintegrated in the oral cavity so that elderly patients can easily take without sticking feeling in their throat. TAK-438 OD tablet, which is able to be taken easily without water, may leads to compliance improvement in elderly patients and those who with limited water intake due to complication such as chronic kidney disease. Therefore, Takeda is considering the development of TAK-438 OD 10 mg and 20 mg tablet as a new formulation corresponding to the strength of TAK-438 10 mg and 20 mg tablet.

4.2 Rationale for the Proposed Study

To develop TAK-438 OD 10 mg and 20 mg, this study was planned to verify the bioequivalence of a single dose of TAK-438 OD 20 mg tablet without water and a single dose of TAK-438 20 mg tablet with water (Study 1) as well as the bioequivalence of a single dose of TAK-438 OD 20 mg tablet with water and a single dose of TAK-438 20 mg with water (Study 2) in healthy adult male subjects (in regard to TAK-438 OD 10 mg, please refer to Section 6.3.2).

4.3 Benefit/Risk Profile

There will be no benefit to subjects in this study other than receiving physical examinations and obtaining information about their general health.

Because TAK-438 (10 mg tablet and 20 mg tablet) has been already approved for marketing and its safety is established, the risk to subject is considered not to exceed the risk of receiving TAK-438.

For further information on TAK-438 OD, please refer to the Investigator's Brochure.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study was designed based on the following hypothesis:

TAK-438 OD 20 mg tablet and TAK-438 20 mg tablet will be shown to be bioequivalent.

5.2 Trial Objectives

5.2.1 Trial Primary Objective

To evaluate the bioequivalence of a single oral administration of a TAK-438 OD 20 mg tablet without water in comparison with TAK-438 20 mg tablet (Study 1), and TAK-438 OD 20 mg tablet with water in comparison with TAK-438 20 mg tablet (Study 2) in Japanese healthy male volunteer subjects.

5.2.2 Trial Secondary Objective

To assess the Pharmacokinetic (PK) parameters other than AUC_{last} and C_{max} of TAK-438F in Japanese healthy volunteer male subjects who take a single oral dose of TAK-438 20 mg.

5.2.3 Safety Objective

To assess the safety in Japanese healthy volunteer male subjects who take a single oral dose of TAK-438 20 mg.

5.3 Endpoints

5.3.1 Primary Endpoint

PK (plasma concentration): AUC_{last} and C_{max} of TAK-438F

5.3.2 Secondary Endpoints

PK (plasma concentration): AUC_{∞}, t_{max}, $MRT_{\infty,ev}$ and λ_z of TAK-438F.

5.3.3 Safety Endpoints

Treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, weight, and electrocardiogram (ECG) parameters

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This study which consists of two studies, Study 1 and Study 2, is a PK study in healthy Japanese subjects to evaluate the bioequivalence of single oral dose of TAK-438 OD 20 mg tablet without water and TAK-438 20 mg tablet with water (Study 1), and TAK-438 OD 20 mg tablet with water and TAK-438 20 mg tablet with water (Study 2) in an open-label and crossover (2x2) design. The safety of TAK-438 OD 20 mg tablet, and TAK-438 20 mg tablet under fasted conditions without breakfast will also be evaluated.

Pilot and Pivotal BE studies are planned for Study 1 and Study 2 in accordance with the "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No.0229-10 dated 29 February 2012) [1] as follows;

Pilot and Pivotal BE studies will be conducted in the same design (inclusion/exclusion criteria, dose, regimen and schedule). Pilot BE studies will be conducted first for the sample size estimation to demonstrate the bioequivalence in Pivotal BE study. Pivotal BE study with the estimated sample size will be conducted to demonstrate the bioequivalence. The data from Pilot BE studies can be merged with the data from Pivotal BE study as needed when the bioequivalence is evaluated. Pivotal BE studies will not be conducted in the case the bioequivalence is demonstrated in Pilot BE study, or the results from Pilot BE study indicate that it is not feasible to demonstrate the bioequivalence.

In the Pilot BE study, 24 subjects will be enrolled in each study (12 subjects in each treatment sequence). Subjects will be randomly assigned to either Treatment Sequences with 1:1 allocation in each study.

In the Pivotal BE study, 26 to 48 subjects will be enrolled in each study (13 to 24 subjects in each treatment sequence depending on outcome of the pilot BE study). Subjects will be randomly assigned to either Treatment Sequences with 1:1 allocation in each study.

In each treatment sequence of Pilot and Pivotal BE studies, subjects will receive a single dose of either of TAK-438 OD 20 mg tablet without water or TAK-438 20 mg tablet with water (Study 1), and either of TAK-438 OD 20 mg tablet with water or TAK-438 20 mg tablet with water (Study 2) on Day 1 in Period 1 and 2. If a subject discontinues from the study, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor. The study site should contact the sponsor for the replacement of subject's treatment assignment and medication identification number.

The planned dose levels and dosing schedules of TAK-438 OD to be evaluated are outlined in Table 6.a.

Table 6.a Dose Levels and Dosing Schedules

Study 1: BE study when administered without water for TAK-438 OD tablet

Pilot BE Study

Sequence	Period 1	Period 2	Number of subjects
A	One TAK-438 OD 20 mg tablet without water	One TAK-438 20 mg tablet with 150 mL water	12
B	One TAK-438 20 mg tablet with 150 mL water	One TAK-438 OD 20 mg tablet without water	12
Dosing Condition: Fasted (without breakfast) condition			

Pivotal BE Study

Sequence	Period 1	Period 2	Number of subjects
A	One TAK-438 OD 20 mg tablet without water	One TAK-438 20 mg tablet with 150 mL water	13- 24
B	One TAK-438 20 mg tablet with 150 mL water	One TAK-438 OD 20 mg tablet without water	13-24
Dosing Condition: Fasted (without breakfast) condition			

Study 2: BE study when administered with water for TAK-438 OD tablet

Pilot BE Study

Sequence	Period 1	Period 2	Number of subjects
C	One TAK-438 OD 20 mg tablet with 150 mL water	One TAK-438 20 mg tablet with 150 mL water	12
D	One TAK-438 20 mg tablet with 150 mL water	One TAK-438 OD 20 mg tablet with 150 mL water	12
Dosing Condition: Fasted (without breakfast) condition			

Pivotal BE study

Sequence	Period 1	Period 2	Number of subjects
C	One TAK-438 OD 20 mg tablet with 150 mL water	One TAK-438 20 mg tablet with 150 mL water	13-24
D	One TAK-438 20 mg tablet with 150 mL water	One TAK-438 OD 20 mg tablet with 150 mL water	13-24
Dosing Condition: Fasted (without breakfast) condition			

6.2 Procedures for Proceeding to the Pivotal Study

In this study, an interim analysis will be performed after the completion of the pilot study to determine whether the results may warrant further analysis in the pivotal study for both Studies 1

and 2. On the basis of bioequivalence assessment in the pilot study, the Sponsor will decide, after discussion(s) with the medical experts, on whether to proceed to the pivotal study and promptly notify the investigator of the decision.

In the case that the results from interim analysis satisfy the criteria of bioequivalence:

The study (Study 1 or 2) will be completed with the pilot study and without implementing the pivotal study.

In the case that the results from interim analysis do not meet the criteria of bioequivalence:

The pivotal study will be implemented after the number of subjects required to conclude the bioequivalence in the study (Study 1 or 2) is calculated based on the results from the pilot study. Any evidence from the pilot study suggesting difficulties in bioequivalence testing in the pivotal study may lead to the pivotal study not being implemented.

Criteria of bioequivalence:

In each of Study 1 and Study 2, the study drugs will be assessed for bioequivalence according to the Guideline for Bioequivalence Studies of Generic Products, [1]. If any of the following criteria is satisfied, TAK-438 OD tablet and TAK-438 tablet will be concluded to be bioequivalent.

- For AUC_{last} and C_{max} of TAK-438F, the two-sided 90% CI of the difference in the means of log-transformed (natural log) parameter between the formulations is between 0.8 and 1.25, inclusive.
- For AUC_{last} and C_{max} of TAK-438F, the difference in the means of log-transformed (natural log) parameter between the formulations is between 0.90 and 1.11, inclusive. Furthermore, the results of the elution test satisfy the requirements specified in the Guideline for Bioequivalence Studies of Generic Products [1].

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Trial Design

The study is planned to evaluate the bioequivalence of TAK-438 OD 20 mg tablet when administered without water (Study 1) or with water (Study 2) compared to TAK-438 20 mg tablet when administered with water in Japanese healthy volunteer male subjects in accordance with the Guideline for Bioequivalence Studies of Generic Products [1].

A 2-period, 2-treatment, cross-over design, which allows bioequivalence evaluation with minimal effect on inter-subject variation, was selected for this study in accordance with the Guideline for Bioequivalence Studies of Generic Products [1].

Open-label design is adopted because the primary objective of the study is to determine the PK profile of TKA-438F, an objective measure.

To eliminate all biases arising from arbitrary assignment of subjects, subjects will be randomized to receive the two treatments in either sequence.

6.3.2 Rationale for Dose

The marketed formulations of TAK-438 are 10 mg and 20 mg tablets. This study is planned to develop both of TAK-438 OD 10 mg and 20 mg tablets for the purpose of making it easier for patients to take their medication.

In this study TAK-438 OD 20 mg tablet is selected to evaluate the bioequivalence when administered with/without water in comparison with TAK-438 20 mg tablet according to the Guideline for Bioequivalence Studies of Generic Products for Different Strengths of Oral Solid Dosage Forms (Pharmaceutical and Food Safety Bureau Notification No. 0229-10 issued on 29 February 2012, Appendix 2) [2], which recommends to conduct a bioequivalence study with the higher strength(ie, TAK-438 OD 20 mg tablet). Also it recommends to evaluate a bioequivalence with the other strength (ie, TAK-438 OD 10 mg tablet) according to the Guideline for Bioequivalence Studies for Different Oral Solid Dosage Forms (Pharmaceutical and Food Safety Bureau Notification No. 0229-10 issued on 29 February 2012, Appendix 4) [3]. The bioequivalence of TAK-438 OD 10 mg and 20 mg tablets will be evaluated in a dissolution test, but not a human bioequivalence study.

6.3.3 Rationale for Washout Period

According to the preceding studies of single and multiple doses of TAK-438, the half-life of TAK-438F was approximately 7 hours (mean) but the half-life of the metabolite (M-I) of TAK-438 was maximum 33.6 hours. Therefore, a 5-fold period (ie, 7 or more days) was adopted in light of feasibility.

6.3.4 Rationale for Endpoints

6.3.4.1 PK Endpoints

AUC_{last} and C_{max} of TAK-438F will be evaluated in accordance with the Guideline for Bioequivalence Studies of Generic Products [1]. The plasma concentration of TAK-438F will be evaluated until 48 hours postdose, the time point when their AUC_{last} is estimated to be over 80% of their AUC_{∞} based on the available PK results.

6.3.4.2 Safety Endpoints

The safety endpoints in this study are the safety variables such as AEs, clinical laboratory tests, vital signs, weight and 12-lead ECG at rest to evaluate the safety following a single dose of TAK-438. They are standard endpoints in the Phase 1 studies in healthy subjects.

6.3.5 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this study, the collection of blood samples for PK evaluation is the critical procedure.

- At any postdose time point, the blood samples for PK evaluation need to be collected as close to the exact nominal time point as possible.

- All other procedures should be completed as close to the scheduled times as possible, either before or after them.
- When other procedures are scheduled at the same time as PK sampling, the blood draw will take priority and other procedures will be performed within an acceptable time window (refer to Appendix B).
- The order of priority can be changed with joint agreement of the investigator and the Sponsor.
- Any unscheduled procedures required for urgently addressing a safety concern will take precedence over all routine scheduled procedures.

6.4 Trial Beginning and End/Completion

6.4.1 Definition of Beginning of the Trial

The overall study begins when the first subject signs the study informed consent form.

6.4.2 Definition of End of the Trial

The overall study ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit (this can be a phone contact), discontinues from the study, or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.4.3 Definition of Trial Discontinuation

Study discontinuation because of nonsafety reasons, such as the following:

- A finding (eg, PK, pharmacodynamic, efficacy, biologic targets) from another nonclinical or clinical study using the study treatment(s) results in the study being stopped for a nonsafety-related reason.
- Data from comparator(s), drug(s) of the same class, or methodology(ies) used in this study become available and results in the study being stopped for a nonsafety-related reason.
- The study is stopped because of nonscientific and nonsafety reason, such as slow enrollment.

Study discontinuation because of safety reasons:

- Early study termination because of unanticipated concerns of safety to the study subjects arising from clinical or nonclinical studies with the study treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

6.4.4 Criteria for Premature Termination or Suspension of the Trial

6.4.4.1 Criteria for Premature Termination or Suspension of Trial

The study will be completed as planned unless 1 or more of the following criteria are met that require temporary suspension or early termination of the study.

1. New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for TAK-438 OD, such that the risk is no longer acceptable for subjects participating in the study.
2. Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
3. Any subject experiences any of the Takeda Medically Significant List events (as outlined in Table 10.a).
4. Liver Function Test (LFT) abnormalities:
    a. Any subject experiences alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN) in the absence of a concomitant bilirubin increase.
    b. Any subject experiences ALT and/or AST >3 × ULN in the presence of a total bilirubin >2 × ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or any other alternative etiology to explain the elevations (ie, Hy's Law cases).
    c. Any subject experiences ALT and/or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

6.4.4.2 Procedures for Premature Termination or Suspension of the Trial

In the event that the Sponsor, the institutional review board (IRB), or the regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the study site during the course of termination or study suspension.

6.4.5 Criteria for Premature Termination or Suspension of the Trial Sites

6.4.5.1 Criteria for Premature Termination or Suspension of the Trial Sites

The study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice, protocol, or contractual agreement, or is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.4.5.2 Procedures for Premature Termination or Suspension of the Trial or the Participation of Trial Sites

In the event that the Sponsor, the IRB, or the regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the study site during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. In the opinion of the investigator or sub-investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject is a healthy Japanese adult male, aged 20 to 60 years, inclusive, at the time of informed consent.
4. The subject weighs at least 50 kg and has a body mass index (BMI) from 18.5 to 25.0 kg/m^2, inclusive at Screening.
5. The subject must be a current nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months prior to the start of study drug administration in Period 1.
6. The subject must be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the Screening Visit and prior to the start of study drug administration in Period 1.

Justifications of the inclusion criteria

Criteria 1, 2, 3, 5 and 6:

These are selected as the standard criteria for the conduct of clinical pharmacological studies in healthy adults.

Criterion 4:

Since whole blood collections of 400 mL from individuals weighing less than 50 kg is harmful to their health, according to Enforcement Regulation on the Law for Securing a Stable Supply of Safe Blood Products, Ministry of Health and Welfare Ordinance No. 22 issued in 1956 [4], the lower weight limit is set to 50 kg. BMI of the subjects are to be within the range of the standard weight according to the Diagnostic Criteria for Obesity proposed by the Japan Society for the Study of Obesity [5].

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 16 weeks (112 days) prior to the start of study drug administration in Period 1.
2. The subject has received TAK-438 in a previous clinical study or as a therapeutic agent.

3. The subject is an immediate family member of or a study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, or endocrine disease or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate in the study or potentially confound its results.
5. The subject has hypersensitivity to any component of TAK-438 OD tablet or TAK-438 tablet.
6. The subject has a positive urine drug result for drugs of abuse at Screening.
7. The subject has a history of drug or alcohol abuse within 2 years prior to the Screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
8. The subject has taken any excluded medication, supplements, or food products during the time periods listed in Section 7.3.
9. The subject has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis), frequent (more than once per week) occurrence of heartburn, or any surgical intervention.
10. The subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1.
11. The subject has a positive test result for hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, or serological reactions for syphilis at Screening.
12. The subject has poor peripheral venous access.
13. The subject has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of study drug administration in Period 1.
14. The subject has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of study drug administration in Period 1.
15. The subject has undergone blood component collection within 2 weeks (14 days) prior to the start of study drug administration in Period 1.
16. The subject has a Screening or Check-in (Day -1) ECG that was abnormal (clinically significant).
17. The subject has abnormal Screening laboratory values that suggest a clinically significant underlying disease or subject with the following laboratory abnormalities: ALT or AST above the ULN.

18. The subject who, in the opinion of the investigator or sub-investigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

Justifications of the exclusion criteria

Criterion 1:

This criterion is meant to ensure the safety of subjects by specifying a minimum interval that they are not affected by any previous clinical study, which is based on the General Considerations for Clinical Trials, Pharmaceutical Safety Bureau Notification No. 380, issued on 21 April 1998 [6].

Criteria 2, 3, 4, 6, 7, 10, 11, 12, and 18:

These are the standard criteria for clinical pharmacological studies in healthy adults and included in consideration of subjects' safety.

Criteria 5, 16, and 17:

These criteria are selected in consideration of subjects' safety.

Criterion 8:

This is a standard criterion for clinical pharmacological studies in healthy adults and included in considerations of subjects' safety and possible effects on PK evaluations.

Criterion 9:

This criterion is selected in considerations of subjects' safety and possible effects on PK evaluations.

Criteria 13 to 15:

These criteria are in accordance with Enforcement Regulation on the Law for Securing a Stable Supply of Safe Blood Products, Ministry of Health and Welfare Ordinance No. 22, issued in 1956 [4].

7.3 Excluded Concomitant Medications, Supplements, Dietary Products

Use of excluded concomitant agents (prescription or nonprescription) or dietary products is outlined in Table 7.a.

Use of prohibited concomitant medications will be allowed when the investigator or sub-investigator deem it necessary to do so for reasons including treatment of an AE.

Table 7.a Excluded Concomitant Medications, Supplements, and Dietary Products

Throughout the study period, beginning from 28 days prior to study drug administration (Day 1) in Period 1	From 7 days prior to study drug administration (Day 1) to discharge in Periods 1 and 2	From 24 hours prior to study drug administration (Day 1) to Discharge in Periods 1 and 2
• Prescription medications • OTC medications • Neutraceuticals (St. John's wort, ginseng, kava kava, ginkgo biloba, and melatonin) • Chinese herbals • Immunization/Vaccines • Nicotine-containing products	• Vitamin supplements • Alcohol-containing products • Grapefruit/grapefruit juice	• Caffeine-containing products

OTC=over-the-counter.

Subjects must be instructed not to take any medications including over-the-counter (OTC) products, without consulting with the investigator or sub-investigator.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

- Diet

  On the day before the visit for blood collection of laboratory tests (Screening visit), the subject must finish the dinner by 21:00, and must fast until blood collection in the next morning. For laboratory tests scheduled in the afternoon on a study visit, blood samples should be collected at least 10 hours after the last meal.
  During confinement, the subjects are to take only served meals and are not allowed to take any other food. Meal menus will be the same for Periods 1 and 2.
  Excessive eating or drinking should be avoided during the study period.

  Dinner will be at approximately 19:00 on the day before study drug administration. The subjects must fast for at least 10 hours prior to and for 4 hours after dosing.
  On the day of the study drug administration, the subjects must not have breakfast. On the day of the study drug administration, the approximate time is 13:00 for lunch and 19:00 for dinner. If the lunch or dinner time conflicts with the laboratory test schedule, the subject must take lunch or dinner promptly after completion of the laboratory tests. On the next day of study drug administration, the approximate time is 9:30 for breakfast, 13:00 for lunch, and 19:00 for dinner. If the breakfast time conflicts with the laboratory test schedule, the subject must take breakfast promptly after completion of the laboratory tests.
  Taking breakfast on Day 3 (the day of discharge) is optional.

- Beverages

  On the day of study drug administration, subjects must not drink any liquid from 1 hour prior to and 4 hours after dosing, with the exception of the water (150 mL) to take the study drug.

- Smoking

  Smoking is not allowed during the study period, beginning from 28 days prior to the start of study drug administration (Day 1).

7.4.2 Activity

Supine position is not allowed for 4 hours after dosing, unless required for examinations, or for other reasons.

Excessive exercise is not allowed during the study period. Subjects should do 15 minutes of light exercise a day during the confinement.

Blood donations are not allowed for at least 12 weeks (84 days) after the final examination in this study. The investigator or sub-investigator will instruct the subjects on the prohibition of blood donations.

If a subject visits another medical institution during the study period, the investigator or sub-investigator should be informed of the visit in advance whenever possible, and should be reported the circumstances and therapy after visit. The investigator or sub-investigator should communicate that medical institution about the subject's participation in the study.

7.5 Documentation of Subjects Failure

The investigator or sub-investigator must account for all subjects who sign informed consent. If a subject is withdrawn from the study before the first study drug administration in Period 1, the investigator or sub-investigator should complete the electronic case report form (eCRF).

The primary reason for subject failure is to be recorded in the eCRF using the following categories:

- Death.
- AE.
- Screen failure (failed inclusion criteria or did meet exclusion criteria) <specify reason>.
- Protocol deviation.
- Lost to follow-up.
- Withdrawal by subject <specify reason>.
- Study terminated by Sponsor.
- Sample size sufficient.
- Other <specify reason>.

Any subject identification number, once assigned to a subject, should not be reused if the assigned subject discontinues the study prior to study drug administration in Period 1. Nevertheless, if a reserve subject is enrolled in the other sequence, the same subject identification number may be used.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the eCRF using the following categories. For the subject who is withdrawn from the study before the first study drug administration in Period 1, refer to Section 7.5.

1. Death.

   The subject died on study.
   Note: If the subject dies on study, the event will be considered as serious adverse event (SAE). Refer to Section 10.2.9.3 for the reporting procedures.

2. AE.

   The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
   Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until the subject's laboratory profile has returned to normal/baseline status, refer to Section 9.2.8), if the following circumstances occur at any time during study drug treatment:

   - LFT abnormalities.
     - ALT or AST >8 × ULN, or
     - ALT or AST >5 × ULN and persists for more than 2 weeks, or
     - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or INR >1.5, or
     - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

3. Protocol deviation.

   The discovery after the first dose of study drug in Period 1 that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

4. Lost to follow-up.

   The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documentation.

5. Withdrawal by subject.

   The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.
   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

6. Study terminated by Sponsor.

   The Sponsor terminates the study.

7. Other

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or sub-investigator may discontinue a subject's study participation at any time during the study if the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or sub-investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

7.8 Subject Replacement

In consideration of possible subject withdrawals for some reasons prior to the study drug administration in Period 1 after Screening, a certain number of individuals judged eligible at Screening are to be retained as standbys only for Period 1. Subject replacement is not allowed for dropouts after the start of study drug administration.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Dosage form:

1. TAK-438 OD 20 mg tablet

   Appearance: white to almost white uncoated tablet
   Content: vonoprazan 20 mg (26.72 mg as vonoprazan fumarate) per tablet
   Chemical name: 1-[5-(2-Fluorophenyl)-1-(pyridine-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine monofumarate
   Generic name: vonoprazan fumarate (JAN)

2. TAK-438 20 mg tablet (Takecab® Tablet 20 mg)

   Appearance: a pale reddish film-coated tablet with a score line on the both sides
   Content: vonoprazan 20 mg (26.72 mg as vonoprazan fumarate) per tablet
   Chemical name: 1-[5-(2-Fluorophenyl)-1-(pyridine-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine monofumarate
   Generic name: vonoprazan fumarate (JAN)

Packaging:

TAK-438 OD 20 mg tablets are to be supplied in a bottle which contains 12 tablets and is to be further packed in a box. TAK-438 20 mg tablets (Takecab® Tablet 20 mg) are to be supplied in commercially available cartons, each of which contains 10 sheets of press through package (PTP), each sheet containing 10 tablets. Each carton is to be labeled “study drug”.

Manufacturing:

TAK-438 OD 20 mg tablets are manufactured by Nipro Pharma Corporation. TAK-438 20 mg tablets (Takecab® Tablet 20 mg) are to be supplied as commercially available Takecab® Tablet 20 mg which will be packed by Spera Pharma Inc.

8.1.1 Clinical Study Drug Labeling

A clinical label will be affixed to study drug containers to indicate that the product is for clinical study, and the study drug name, the Sponsor and its address, the manufacturing number, the method for storage, and the expiration date.

8.1.2 Clinical Study Drug Inventory and Storage

All the study drugs are to be stored at room temperature (1°C to 30°C).

The study drugs must be kept in an appropriate, limited-access, secure place until it is used or returned to the Sponsor or designee for destruction. The study drugs must be stored under the conditions specified on the label until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.4 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (the site designee) will receive a pharmacy manual created by the Sponsor, and follow the manual for storage and accountability of the Sponsor-supplied drug supplies. The investigator will receive the manual from the Sponsor as well. The manual will provide instructions on ensuring appropriate receipt, handling, storage, accountability, and dispensation of the Sponsor-supplied drug. The manual will also describe procedures for the collection of unused medications from the subject and their return to the Sponsor, or the destruction of any unused supplies.

The on-site pharmacist (the site designee) will immediately return any unused study drugs in a sealed package to the Sponsor after the study is closed at the study site.

9.0 STUDY PROCEDURES

The investigator or sub-investigator should collect data according to the procedures described in the following sections. For each procedure, subjects are to be assessed by the same investigator, sub-investigator or site designee whenever possible. The Schedule of Study Procedures is located in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent

Informed consent must be obtained before the subject enters into the study and before any protocol-directed procedures are performed. The requirements of informed consent are described in in Section 13.2.

9.1.1.1 Assignment of Subject Identification Numbers

A unique subject identification number will be assigned to each subject at the time that informed consent is explained; this subject identification number will be used throughout the study.

9.1.1.2 Study Drug Assignment

The investigator or sub-investigator will assign the study drugs to subjects who are judged eligible based on the examinations prior to study drug administration (eg, screening and laboratory tests). For each study and sequence, the subjects will be assigned to the study drug in ascending order of their subject identification number according to the randomization schedule.

Subjects will be assigned to receive a 5-digit medication identification number in which ten-thousands digit represents the study type, thousands digit represents the sequence of the crossover study, and the remaining digits represents the sequential number within each sequence. The 5-digit number will be used by the study site to identify the PK samples, and will be the only subject identifier used on all PK sample collections. It should also be indicated on the PK sample vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results instead of the subject identification number. It does not replace the last 3 digit numbers of the subject identification number. In case of subject replacement, the study drug with a medication identification number for the withdrawn subject will be used by the replacing subject. The investigator or its designee will record the medication identification number in the eCRF.

9.1.2 Inclusion and Exclusion Criteria

Each subject will be assessed according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demographics

Demographic information to be obtained will include date of birth, sex, race as described by the subject, height, weight, caffeine use, alcohol use, and smoking classification of the subject.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that resolved within 1 year prior to the signing of informed consent. Ongoing conditions will be considered concurrent medical conditions, which should include clinically significant laboratory, 12-lead ECG, or physical examination abnormalities noted at screening/baseline examination. Any concurrent medical conditions (ie, diagnoses) should be described. Medication history to be obtained will include any medication relevant to eligibility criteria and safety evaluations stopped at or within 4 weeks (28 days) prior to the signing of informed consent.

9.1.4 Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the Sponsor. Subjects will be asked whether they have taken any medication other than the study drug (used from the signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication names, route of administrations, start and end dates, and reasons for use.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

9.2.2 Height and Weight

Each subject should have his height and weight measured. Height will be recorded in centimeters without decimal places (rounding off the first decimal place). Weight will be collected in kilograms (kg) with the first decimal place (rounding off the second decimal place).

9.2.3 BMI

Body mass index equals a subject's weight in kilograms divided by height in meters squared (body mass index=kg/m^2).The values should be calculated to the first decimal place (rounding off the second decimal place). A subject's eligibility with respect to the BMI is determined based on the rounded off value. BMI will not be recorded in the eCRF.

9.2.4 Vital Signs

Vital signs will include body temperature (axilla measurement), respiratory rate, supine blood pressure (systolic and diastolic, after resting more than 5 minutes), and pulse (beats per minute).

The same method (eg, the same and appropriately sized cuff, manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects. All measurements will be recorded on the source documents and in the eCRF.

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within an acceptable time window (refer to Appendix B).

9.2.5 12-Lead ECG

A 12-lead ECG will be recorded. Subjects should be resting in a supine position for at least 5 minutes before each ECG recording. The investigator or sub-investigator (or a qualified cardiologist at the study site) will interpret the ECG using one of the following categories: normal or abnormal. If an ECG is abnormal, the investigator or sub-investigator (or a qualified cardiologist at the study site) will judge clinical significance of the abnormality. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and corrected QT interval using Fridericia's formula (QTcF).

9.2.6 Study Drug Administration

Each subject will receive the study drug in Periods 1 and 2 as described below. The administration conditions will be the same for the pilot and pivotal studies in Studies 1 and 2.

Study 1: The subject will orally receive one TAK-438 OD 20 mg tablet without water or one TAK-438 20 mg with 150 mL of water under fasted (without breakfast [after at least 10 hours of fasting]) condition. TAK-438 OD 20 mg tablet should not be swallowed whole, but be allowed to dissolve in the mouth without the tablet being chewed and then swallowed with the saliva. TAK-438 20 mg tablet should be swallowed whole with water.

Study 2: The subject will orally receive one TAK-438 OD 20 mg tablet, or one TAK-438 20 mg tablet with 150 mL of water under fasted (without breakfast [after at least 10 hours of fasting]) condition. The tablets should be swallowed whole with water.

9.2.7 Adverse Event Monitoring

AE monitoring begins after signing of the informed consent form. A complete description of adverse event collections and procedures is provided in in Section 10.2.

9.2.8 Laboratory Procedures and Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Samples will be collected following a minimum 10-hour fast on the days stipulated in the Schedule of Study Procedures (Section 3.0).

9.2.8.1 Clinical Laboratory Tests

Hematology

The hematology assessment will include the following tests:

RBC
WBC count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
Hemoglobin
Hematocrit
Platelets

Chemistry

The chemistry assessment will include the following tests:

ALT
Albumin
ALP
AST
Total bilirubin
Total protein
Creatinine
BUN
Creatine kinase
GGT
Potassium
Sodium
Fasting glucose
Chloride

Urinalysis

The urinalysis assessment will include the following tests:

pH
Specific gravity
Qualitative tests for protein
Qualitative tests for glucose

Other

Tests performed at eligibility assessment:
Serum
Immunology tests: HBsAg, HCV antibody, HIV antigen/antibody, serum test for syphilis
Urine
Urine drug tests: phencyclidine, benzodiazepines, cocaine, antihypnotic agents, cannabinoids, opioids, barbiturates, and tricyclic antidepressants

HBsAg= hepatitis B virus surface antigen, HCV= hepatitis C virus, HIV= human immunodeficiency virus, RBC=red blood cells, WBC=white blood cells.
Note: The investigator or sub-investigator will report the results of immunology and urine drug screen directly to subjects. The Sponsor will confirm the overall test results (as "Positive" or "All negative"), rather than detailed results, for subjects (including reserve subjects) to be administered the study drug.

The local laboratory will perform laboratory tests for hematology, chemistry, and urinalysis. The results of laboratory tests will be returned to the investigator or sub-investigator, who is responsible for reviewing and filing these results.

If subjects experience an ALT or AST of >2 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase [ALP], ALT, AST, total bilirubin, gamma-glutamyl transferase [GGT], and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

Refer to Sections 10.2.9.3 and 10.2.9.4 for the appropriate guidance on reporting abnormal LFTs as SAEs or AESIs.

The investigator will maintain a copy of the reference ranges for the laboratory used.

9.3 PK Samples

Samples for PK analyses will be collected as specified in the Schedule of Study Procedures (Section 3.0). Please refer to the separately created procedure for information on the collection, processing, and shipment of samples to the central laboratory. The actual time of sample collection for PK analyses will be recorded on source documents and the eCRF.

Primary specimen collection parameters are provided in Table 9.a.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Plasma sample for TAK-438 PK	Plasma	PK analysis	Mandatory

9.3.1 PK Measurements

The PK parameters of TAK-438F will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations.

The following PK parameters will be calculated from plasma concentrations of TAK-438F, unless otherwise specified:

Symbol/Term	Definition
Plasma	
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the concentration-time curve from time 0 to infinity.
C_{max}	Maximum observed concentration.
t_{max}	Time of first occurrence of C_{max}.
$t_{1/2z}$	Terminal disposition phase half-life.
λ_z	Terminal disposition phase rate constant.
$MRT_{\infty,ev}$	Mean residence time after extravascular administration from time 0 to infinity.

9.3.1.1 Plasma for PK Measurements

Blood samples for PK analyses of TAK-438F (one 4-mL sample per scheduled time) will be collected in Vacutainers.

Blood samples for PK analyses of TAK-438F will be collected according to the schedule described in Table 9.b.

Table 9.b Collection of Blood Samples for PK Analysis

Analyte	Matrix	Study Day	Scheduled Time
TAK-438F	Plasma	Days 1 to 3	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose

If a subject is prematurely withdrawn from the study after the start of study drug administration, a blood sample at the time of early termination will be collected as follows.

In Studies 1 and 2, blood sample for PK analysis of TAK-438F will be collected only if the subject is withdrawn from the study within 48 hours after the start of study drug administration.

9.3.1.2 Analytical Methods Used for PK Samples

Plasma concentrations of TAK-438F will be measured using liquid chromatography-tandem mass spectrometry (LC/MS/MS).

9.3.2 Confinement

In both Studies 1 and 2, each subject will be checked-in to the study site on Day -1 and hospitalized until 48 hours postdose on Day 3. Subjects will undergo daily examinations, observations, and assessments as specified in the Schedule of Study Procedures in Section 3.0. Subjects will be discharged after being confirmed by physical examination and tests on Day 3 to have no significant abnormality in his health.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment or study participation.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study participation, whether or not it is considered related to the drug or study procedure.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator or sub-investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters may be considered AEs if they are judged to be clinically significant by the investigator or sub-investigator (ie, if some action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc.) should NOT be recorded as an AE unless related to a

study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators or sub-investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators or sub-investigators should ensure that the AE term recorded captures the change from baseline in the condition (eg, "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators or sub-investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study drug or after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators or sub-investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study drug, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator, sub-investigator, or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE page of the eCRF according to Section 10.0.
- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.9.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
	Acute liver failure
Torsade de pointes/ventricular fibrillation/ ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures (including convulsion and epilepsy)	Pulmonary fibrosis (including interstitial lung disease)
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome)	Neuroleptic malignant syndrome/malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.1.2 Special Interest AEs

A special interest AE (serious or non-serious) is an event of concern specific to the study drug. The special interest AEs in this study will be defined as liver dysfunction, gastrointestinal *Clostridium difficile* infection, and hypersensitivity.

The investigator and sub-investigator will monitor the subject for the occurrence of special interest AEs. An occurrence of any special interest AE should be reported according to the procedure described in Section 10.2.9.4. Such events may require further investigation to establish their evaluation.

10.1.2.1 Liver Dysfunction

Liver dysfunction is defined as follows:

- ALT or AST >2 × ULN, or
- Total bilirubin >2 × ULN

A Liver Dysfunction Form must be completed with relevant detailed information on the subject, possible alternative etiologies (eg, acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions), clinical course, and action taken for the event. Refer to Section 9.2.8.1 for the follow-up laboratory testing.

10.1.2.2 Gastrointestinal Clostridium difficile Infection

Gastrointestinal *Clostridium difficile* infection is defined as follows:

- An AE with any of the following preferred terms (PT) of the Medical Dictionary for Regulatory Activities (MedDRA) Ver. 21.0: Clostridial infection, Clostridium bacteraemia,

Clostridium colitis, Clostridium difficile colitis, Clostridium difficile infection, Clostridial sepsis, Clostridium test positive, Gastroenteritis clostridial, or pseudomembranous colitis.

A Gastrointestinal *Clostridium difficile* Infection Form must be completed with relevant detailed information on the subject, possible alternative etiologies (eg, concomitant use of antibacterial agents or immunosuppressive agents, or medical history/concurrent medical conditions), the clinical course, and action taken for the event.

10.1.2.3 Hypersensitivity

A hypersensitivity-related AE is defined as follows.

- An AE related to hypersensitivity (eg, anaphylactic reaction, angioedema, erythema multiforme, urticaria, or rash) that led to discontinuation of the study drug.

A Hypersensitivity Form must be completed with relevant detailed information on the subject, possible alternative etiologies, the clinical course, and action taken for the event.

The special interest AEs should be record as AEs in the eCRF. The completed eCRF along with all other required documentation should be submitted to the Sponsor.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild:	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe:	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The causal relationship of each AE to study drug(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Assigning Causality of AEs to Study Procedures

The causal relationship of each AE to study procedures will be assessed.

The causality of an event should be assessed as Related if the investigator or sub-investigator considers that there is a reasonable possibility that the event is due to a study procedure. Otherwise, the causality should be assessed as Not Related.

10.2.4 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject, investigator, or sub-investigator.

10.2.5 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.6 Pattern of Adverse Event (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous".

10.2.7 Action Taken with Study Treatment

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require changing the dose of study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug had not yet started or dosing with study drug was already stopped before the onset of the AE.

10.2.8 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.9 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent and continue until the end of examination at 48 hours postdose in Period 2.

10.2.9.2 Reporting AEs

At each study visit, the investigator or sub-investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

Subjects experiencing an SAE prior to the first exposure to study drug must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin prior to the first exposure to study drug, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the

investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Investigator's or sub-investigator's opinion of the causal relationship between the event and administration of study drug(s).
- Investigator's or sub-investigator's opinion of the causal relationship to study procedure(s), with a description of the suspected procedure.
- Action taken with the study drug(s).
- Outcome of event.
- Seriousness.
- Special Interest AEs.
- Timing of occurrence (after administration of study drug[s]).

10.2.9.3 Reporting SAEs

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

An SAE should be reported by the investigator or sub-investigator to the Sponsor within 1 business day of the first onset or notification of the SAE, along with any relevant information. The investigator should submit a detailed SAE Form to the Sponsor within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's or sub-investigator's name.
- Name of the study drug(s).
- Causality assessment.

Any SAE spontaneously reported to the investigator or sub-investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator or sub-investigator should complete a follow-up SAE form copy or provide other

written documentation and promptly submit to the Sponsor. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.2.9.4 Reporting Special Interest AEs

When a special interest AE (refer to Section 10.1.2) occurs through the AE collection period, it should be reported by the investigator or sub-investigator to the Sponsor within 1 business day of the first onset or notification of the event, along with any relevant information. The investigator should also submit a Special Interest AE Form to the Sponsor within 10 business days. Additionally, the investigator should submit the original copy of the Special Interest AE Form to the Sponsor.

The special interest AEs should be record as AEs in the eCRF.

10.2.9.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.9.3. The investigator or sub-investigator must report to the study monitor and evaluate relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease, or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.2.8 must also be performed.

10.2.10 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs, and the head of the study site. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definitions of analysis variables, and analysis methodologies to address all study objectives.

After the database of the pilot study is locked for all the subjects' data, statistical analysis will be performed on available data. In the case that the pivotal study is implemented, statistical analysis will also be performed on data from the pivotal study after the database of the pivotal study is locked for all of the subjects' data.

11.1.1 Analysis Sets

In this study, 2 analysis sets are defined: the safety analysis set and PK analysis set. The definition of each analysis set will be described in the SAP.

The Sponsor will verify the validity of the definitions of the analysis sets and the rules for handling data in consultation with a medical expert, as needed. The Sponsor will address all remaining uncertainties not specified at planning, and will finalize the SAP prior to the database lock.

11.1.1.1 Safety Analysis Set

The safety analysis set will be defined as all subjects who received at least one dose of study drug.

11.1.1.2 PK Analysis Set

The PK analysis set will be defined as all subjects who received at least one dose of study drug, and whose PK data are evaluable.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the safety analysis set and PK analysis set.

11.1.3 PK Analysis

11.1.3.1 PK Endpoints and Its Analytical Methods

The primary endpoint of the study is:

PK (plasma concentration)

- AUC_{last} and C_{max} of TAK-438F.

The secondary endpoints of the study are:

PK (plasma concentration)

- AUC_{∞}, t_{max}, $MRT_{\infty,ev}$, and λ_z of TAK-438F.

Analytical methods:

The following analyses will be separately conducted using the PK analysis set for each study (Study 1 and Study 2).

1) Plasma concentrations

   At each time point scheduled for blood sampling, descriptive statistics of plasma concentrations of TAK-438F will be provided for each formulation (ie, TAK-438 OD tablet and TAK-438 tablet). Case plots and mean plots with standard deviations (SD) will be provided for each formulation. Descriptive statistics of PK parameters will be provided for each formulation. Additionally, descriptive statistics will be provided for AUC_{last} and C_{max} ratios (TAK-438 OD tablet/TAK-438 tablet).

2) Testing for bioequivalence:

   For log-transformed (natural log) AUC_{last} and C_{max} of TAK-438F (ie, the primary endpoint of the study), the two-sided 90% CI of the difference in the least square means between the formulations (TAK-438 OD tablet – TAK-438 tablet) will be provided using the analysis of variance (ANOVA) model. The same analyses will be performed for untransformed AUC_{last} and C_{max}.
   The same analyses will also be performed for AUC_{∞}, t_{max}, $MRT_{\infty,ev}$, and λ_z (ie, the secondary endpoint of the study) to provide additional information.

11.1.3.2 Methods of Data Conversion and Handling of Missing Data

For plasma concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero. The details will be provided in the SAP.

11.1.4 Safety Analysis

11.1.4.1 Safety Endpoints and Analytical Methods

Safety endpoints will be the following:

TEAEs, clinical laboratory tests, vital signs, weight, and 12-lead ECG.

Analytical methods:

The following analyses will be separately conducted using the safety analysis set for each study (Study 1 and Study 2).

1) TEAEs

   A TEAE is defined as an AE with a date of onset that occurs on or after the start of study drug administration. The analyses of TEAEs will be conducted for the following. TEAEs will be coded using the MedDRA dictionary and tabulated by system organ class (SOC) and PT for each formulation:

   - The frequency of all TEAEs

- The frequency of drug-related TEAEs
- The frequency of TEAEs by intensity
- The frequency of drug-related TEAEs by intensity
- The frequency of serious TEAEs

2) Clinical laboratory tests

   For continuous variables, descriptive statistics of observed values and changes from baseline will be provided for each scheduled time point by formulation. Case plots of observed values will be provided for each formulation.
   For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled time point will be provided for each formulation.

3) Vital signs and weight

   For continuous variables, descriptive statistics of observed values and changes from baseline will be provided for each scheduled time point by formulation. Case plots of observed values will be provided for each formulation.

4) Other safety parameters

   12-lead ECG parameters will be summarized as follows:
   For continuous variables, descriptive statistics of observed values and changes from baseline will be provided for each scheduled time point by formulation. Case plots of observed values will be provided for each formulation.
   For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled time point will be provided for each formulation.

11.2 Interim Analysis and Criteria for Early Termination

After the completion of the pilot study, an analysis will be separately conducted for each study (Study 1 and Study 2) on data obtained from the pilot study to determine whether the results may warrant further analysis in the pivotal study. On the basis of bioequivalence assessment in the pilot study, the Sponsor will determine entry into the pivotal study after discussion(s) with the medical experts, and will promptly notify the investigator. Refer to Section 6.2 for the procedures for proceeding to the pivotal study.

11.3 Determination of Sample Size

In Studies 1 and 2, the planned number of subjects is 12 per sequence (total of 24 subjects) in the pilot study, and 24 per sequence (total of 48 subjects) in the pivotal study. Statistical basis for the sample size is presented below.

Assuming a root mean square error of 0.195 for PK parameters in the pilot study, the power of two one-sided t-tests to verify the bioequivalence [H_0: $\ln(\mu)\leq\ln(\theta_1)$, $\ln(\mu)\geq\ln(\theta_2)$; H_1: $\ln(\theta_1)<\ln(\mu)<\ln(\theta_2)$; where $\mu=\mu_t/\mu_s$, μ_t is the mean for TAK-438 OD tablet, μ_s is the mean for the concomitant administration of TAK-438 tablet, $\theta_1=0.80$, and $\theta_2=1.25$] at a one-sided significance

level of 5% and μ=0.95 to 1.05 would be ≥90% with a sample size of 12 subjects per sequence (total of 24 subjects).

In the case that the pivotal study will be implemented, the number of subjects will be recalculated based on the results from the pilot study. Assuming a maximal root mean square error of 0.195 for PK parameters in the pivotal study, two one-sided t-tests with a one-sided significance level of 5% and μ=0.90 to 1.11 would need a maximum of 24 subjects per sequence (total of 48 subjects) to provide 90% power to verify the bioequivalence.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the Sponsor or its designee (contract research organization [CRO]) and by the IRB.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee, including but not limited to the Investigator's Binder, trial drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator or sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the Sponsor or a prior approval from IRB. In the event of a deviation or change, the investigator should notify the Sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the Sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The investigator and the head of the study site guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A.

13.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The Sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The Sponsor will notify study site once the Sponsor has confirmed the adequacy of study site regulatory documentation. Until the site receives notification no protocol activities, including screening, may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and Sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given.

The informed consent form will detail the requirements of the participant and the fact that he is free to withdraw at any time without giving a reason and without prejudice to his further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the Sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject determines he will participate in the study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed by the investigator or sub-investigator to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

13.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy

reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (refer to Section 13.2).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the Sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. The investigator or sub-investigator needs to obtain a prior written approval from the Sponsor to publish any information from the study externally, such as to a professional association.

13.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with facility name, investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

13.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the study site where the subject is participating. If a local underwriter is required, then the Sponsor or Sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the Sponsor's policy on subject compensation and treatment for injury. If the investigator or sub-investigator has questions regarding this policy, he or she should contact the Sponsor or Sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

A separate contact information list (Protocol Annex 1) will be provided to the study site.

14.1.2 Investigator Agreement

A separate agreement will be provided to the study site.

14.1.3 Study-Related Responsibilities

A separate contact information list (Protocol Annex 1) will be provided to the study site.

14.1.4 List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	international normalized ratio
IRB	institutional review board
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TAK-438F	TAK-438 free base
ULT	upper limit of normal

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

The Sponsor or its designee will supply study sites with access to eCRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the study site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded in the eCRFs:

- Laboratory results
- Measurement results of drug concentrations

After the lock of the clinical study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or sub-investigator with use of change and modification records of the eCRFs. The investigator must review the data change for completeness and accuracy, and must e-sign.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the Sponsor or its designee. The Sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

15.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated

informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees.

The investigator and the head of the study site are required to retain relevant essential documents until the day specified as 1 or 2 below, whichever comes later. However, if the Sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the Sponsor.

1. The day on which marketing approval for the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion for the study.

In addition, the investigator and the head of the study site should retain the relevant essential documents until the receipt of a Sponsor-issued notification that states the retention is no longer required.

16.0 REFERENCES

1. Guideline for Bioequivalence Studies of Generic Products, Pharmaceutical and Food Safety Bureau Notification No. 0229-10 (February 29, 2012).
2. Guideline for Bioequivalence Studies of Generic Products for Different Strengths of Oral Solid Dosage Forms, Pharmaceutical and Food Safety Bureau Notification No. 0229-10 (February 29, 2012).
3. Guideline for Bioequivalence Studies for Different Oral Solid Dosage Forms, Pharmaceutical and Food Safety Bureau Notification No. 0229-10 (February 29, 2012).
4. Enforcement Regulation on the Law for Securing a Stable Supply of Safe Blood Products, Ministry of Health and Welfare Ordinance No. 22 (25 June 1956).
5. Japan Society for the Study of Obesity. Diagnostic Criteria for Obesity 2011. Journal of Japan Society for the Study of Obesity 2011 (Extra Edition).
6. General Considerations for Clinical Trials, Pharmaceutical Safety Bureau Notification No. 380 (21 April 1998).

An Open-Label, Crossover Phase 1 Study to Evaluate the Bioequivalence of TAK-438 OD (Orally Disintegrating) Tablet When Administered without Water (Study 1) or with Water (Study 2) and TAK-438 tablet in Healthy Adult Male Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	PPD	PPD
PPD	PPD	PPD
PPD	PPD	PPD